Remarks

I. Status of the Claims

Upon entry of the foregoing amendment, claims 109-128 and 130-142 are pending in the application, with claims 109, 110, and 118 being the independent claims. New claims 140-142 are added. Claims 109, 110, 118, 122, 124, 133, 137, and 138 are amended. Claim 129 is canceled. Claims 1-108 were canceled previously. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. The Amendments

The pending claims are directed to a glycoengineered, recombinant antibody comprising an *IgG* Fc region containing N-linked oligosaccharides, wherein the antibody is isolated from a *mammalian host cell* and has been engineered to have an *increased proportion of nonfucosylated oligosaccharides in the Fc region (i.e., oligosaccharide conformations that lack the fucose residue) compared to the corresponding antibody produced by the same host cell that has not been glycoengineered*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim 110) as a result of said increased proportion of nonfucosylated oligosaccharides. Support for the amendments and new claims can be found *inter alia* in the disclosure as follows:

CLAIM	SUPPORT
109, 110, 118	See, for example, page 7, line 33 through page 8, line 1; page 17, lines 29-33; page 15, lines 5-8; page 21, line 15 through page 22, line 22; and Examples 3 and 4.
122, 124, 133	See, for example, page 7, line 33 through page 8, line 1; and page 17, lines 29-33.
137	See, for example, page 37, lines 19-21

138	See, for example, page 22, line 33 through page 23, line 11.
140	See, for example, page 15, lines 5-8; page 21, line 15 through page 22, line 22; and Examples 3 and 4.
141, 142	See, for example, page 7, lines 14-16; and page 21, lines 15-25.

Accordingly, no new matter is believed to have been added by the amendments, and their entry is respectfully requested.

III. Brief Description of the Invention

The presently claimed invention is directed to a glycoengineered, recombinant antibody comprising an *IgG* Fc region containing N-linked oligosaccharides, wherein the antibody is isolated from a *mammalian host cell* and has been engineered to have an *increased proportion of nonfucosylated oligosaccharides in the Fc region compared to the corresponding antibody produced by the same host cell that has not been glycoengineered*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim 110) as a result of said increased proportion of nonfucosylated oligosaccharides. This invention is the result of Applicants' discovery that the oligosaccharides that occur in the Fc region of antibodies, such as IgG, can be engineered, by a variety of methods, to produce non-naturally occurring *variant* oligosaccharide conformations that have been found to dramatically increase the antibody effector function, such as antibody-dependent cellular cytotoxicity (ADCC), as well as the antibody's affinity for Fc receptors.

Typically, there is heterogeneous processing of the core oligosaccharide structures attached at a particular glycosylation site, so that even monoclonal antibodies exist as multiple glycoforms. By engineering the host cells that produce the antibodies to

favor production of an antibody having a variant oligosaccharide conformation in the Fc region, *i.e.*, having a significant increase in the proportion of nonfucosylated oligosaccharide structures, Applicants are able to generate variant glycoforms of the antibody having oligosaccharide conformations that are *not capable of being produced by the host cell absent the glycoengineering* and which exhibit dramatically increased ADCC and Fc receptor binding compared to the corresponding nonglycoengineered antibody.

IV. The Rejections

A. The Rejections Under 35 U.S.C. § 112, First Paragraph

1. Rejection of Claims 137 and 138--New Matter

At paragraph 6 on page 3 of the Office Action, the Office has indicated that claims 137 and 138 are rejected under the first paragraph of 35 U.S.C. § 112 for failing to comply with the written description requirement because they allegedly introduce new matter. Applicants respectfully traverse this rejection.

Claim 137 is directed to an antibody "wherein at least 45% of the oligosaccharides in the Fc region are complex structures." The Office asserts that the portion of the specification identified by Applicants as support for this recitation "fails to support the full scope of the newly entered claim. Indeed this portion of the specification teaches that '45 to 50%' is achieved. The claim encompasses an open-ended amount and as such introduces impermissible new matter, not supporte[d] by the originally filed specification." Office Action at page 3, paragraph 7. Applicants respectfully disagree with this assertion. Nevertheless, solely in an effort to facilitate prosecution, and not in acquiescence to the Office's rejection, claim 137 has been amended. Accordingly,

Applicants believe that the rejection has been rendered moot and respectfully request that it be reconsidered and withdrawn.

Claim 138 is directed to an antibody, "wherein said glycoengineered, recombinant antibody exhibits at least an 80% increase in maximal ADCC activity." The Office asserts that the portion of the specification identified by Applicants as support for this recitation "teaches that 'almost 80%' can be achieved. Thus claim 138 does not find support in the specification and as such introduced impermissible new matter." Office Action at page 3, paragraph 8. Applicants respectfully disagree with this assertion. Nevertheless, solely in an effort to facilitate prosecution, and not in acquiescence to the Office's rejection, claim 138 has been amended. Accordingly, Applicants believe that the rejection has been rendered moot and respectfully request that it be reconsidered and withdrawn.

2. Rejection of claims 109-139--Written Description

At paragraph 9 on page 4 of the Office Action, the Office indicates that claims 109-139 are rejected under the first paragraph of 35 U.S.C. § 112 for allegedly failing to comply with the written description requirement. The Office asserts that "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Office Action at page 4, paragraph 9. Applicants respectfully traverse this rejection.

To meet the written description requirement, an applicant's disclosure must convey with reasonable clarity to one skilled in the art that, at the time of filing the application, the applicant was in possession of the claimed invention. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); *In re Wertheim*, 541 F.2d 257,

262 (C.C.P.A. 1976*); In re Smythe*, 480 F.2d 1376, 1382 (C.C.P.A. 1973). Possession is shown "by such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). However, "the invention claimed does not have to be described *in ipsis verbis* in order to satisfy the [written] description requirement of § 112." *In re Lukach*, 442 F.2d 967, 969 (C.C.P.A. 1971); *see also Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Likewise, an adequate written description does *not* require examples or actual reduction to practice, and "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). Furthermore, "[t]he descriptive text needed to meet [the written description requirement] varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar,* 418 F.3d 1349, 1357. There is no need to re-describe what is already known. *See id.*

In the present case, the Office asserts that the "description as filed only provides sufficient written support for production of antibodies with altered glycosylation that were produced in CHO cells expressing GnT III," and alleges that there is no disclosure of any other modified cell type besides CHO cells that would produce recombinant antibodies with an increased proportion of nonfucosylated oligosaccharides resulting in increased ADCC relative to an unmodified cell. Office Action at page 4, paragraph 10.

Applicants respectfully submit that, to the extent that the Office is suggesting that an adequate written description requires examples or actual reduction to practice for every embodiment of the invention, or recitation of a known structure, such requirements

are legally incorrect. *See Falkner*, 448 F.3d at 1366. In any event, as discussed below, the disclosure of the present application provides ample written description support such that one of ordinary skill in the art would have understood that Applicants had possession of the claimed invention at the time the application was filed.

a) The Claims Are Directed to a Finite and Well-Defined Genus of Antibodies

The Office appears to be of the position that the claimed invention embraces a vast, undefined, and widely variant genus with respect to cell types and glycoprotein-modifying glycosyltrasferases. *See* Office Action at pages 5-6. Specifically, the Office asserts that "[w]ith respect to a required description of a representative number of species of multiple cell types modified with a variety of different glycosyltransferases, a review of the state of the prior art appears to indicate that glycosylation patterns due to unmodified cells and indeed the differences that that could be expected with modification by different glycosyltransferases remains unclear and complex at the time the invention was made." *Id.* Applicants respectfully disagree with these assertions.

The written description requirement for a genus can be satisfied by sufficiently describing a representative number of species. *See* MPEP § 2163 (Rev. 3, Aug. 2005) at 2100-182. "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus in view of the species disclosed." *Id.* at 2100-183. In determining whether written description for a genus is sufficient, the knowledge of one skilled in the art must be considered. *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1126 (Fed. Cir. 2004).

As discussed below, Applicants respectfully submit that the genera of host cells, IgG Fc regions, oligosaccharide structures, and glycosyltransferases encompassed by the claimed invention are not infinite or widely variant. Furthermore, given the knowledge in the art, that the members of these genera would be identifiable and recognizable to one of ordinary skill in the art based on the information provided in the specification as filed. *See, e.g., Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d 1313 (Fed. Cir. 2003).

(1) The Claims are Directed to Antibodies with Common Structural Features

On page 5 of the Office Action, the Office suggests that the claimed antibodies are not linked by common molecular structures or components "that are linked in order to exhibit the disclosed biological functions." Applicants disagree. In fact, the common structural features are explicitly recited in the claims. Specifically, the claims are directed to 1) IgG antibodies 2) having an Fc region containing N-linked oligosaccharides 3) that have been glycoengineered to have *an increased proportion of nonfucosylated residues*. The Fc region of IgG antibodies is well-characterized. As discussed in detail below, the oligosaccharides structures found in antibody Fc regions are likewise well-characterized. Finally, the claims are limited to antibodies that have been glycoengineered to have an increased proportion of nonfucosylated oligosaccharides in the Fc region, which Applicants have demonstrated results in increased ADCC and Fc receptor binding. Thus, contrary to the Office's assertion, the claimed genus of antibodies all share readily identifiable structural features relating to the desired biological function of increased ADCC and increased Fc receptor binding.

(2) The Genus of Mammalian Host Cells is Well-Defined and Recognizable to One of Ordinary Skill in the Art

The amended claims recite that the recombinant, glycoengineered antibodies are isolated from *mammalian* host cells. By knowing that a cell type is derived from a mammalian source, one of ordinary skill in the art would know that it has features in common with other mammalian cell lines; in particular, its ability to glycosylate proteins in a particular and defined manner. For example, Jenkins *et al.* provide a table summarizing major glycosylation characteristics of different cell types. Jenkins *et al.*, *Nature Biotech.* 14: 975, 976 (1996) (of record as Document AS19, and attached hereto as EXHIBIT A). Therein it is shown that, of the various mammalian cell types tested (*e.g.*, hamster, mouse, rat, goat & sheep, and human), most show the same types of N-linked glycosylation (*e.g.*, oligo-mannose and complex glycosylation are present, but not hyper-mannose glyocsylation). *Id.* Thus, the members of the genus of mammalian cell types encompassed by the claimed invention have common features that could be recognized and identified by one of ordinary skill in the art, and that make this a well-defined genus.

(3) The Point of N-linked Oligosaccharide Attachment in the IgG Fc Region Does Not Vary

The amended claims also recite that the Fc region containing N-linked oligosaccharides is an immunoglobulin G (IgG) Fc region. Glycosylation in the IgG Fc region occurs at a single conserved asparagine amino acid residue: Asn297 in the C_H2 domain. *See, e.g.*, Specification at page 21, lines 19-20. One of ordinary skill would have known that "[t]he Fc glycosylation site is a conserved feature for all mammalian IgGs investigated..." *See, e.g.*, Jefferis and Lund, *Chem. Immunol.* 65: 111-128, 113

(1996) (attached hereto as EXHIBIT B). Since the N-linked oligosaccharides in the Fc region are all attached to Asn297 (or the residue that corresponds thereto when the Fc region comprises an IgG fragment), the point of attachment for the core N-linked oligosaccharide structure does not vary at all. Hence, the IgG Fc region containing N-linked oligosaccharides clearly is not an infinite or widely variant genus.

(4) The Genus of Possible Oligosaccharide Structures is Defined and Finite

The genus of possible N-linked oligosaccharides encompassed by the claimed invention is also not infinite or widely variant. Rather, this is a well-defined genus encompassing members that are known in the art. In particular, all mature N-linked oligosaccharides have the same common core structure of Man_3GlNAc_2. *See* Jenkins EXHIBIT A at 975, first column. Furthermore, the different glycoforms of a glycoprotein are based on the same pool of common oligosaccharide structures: mannose (Man), and N-acetylglucosamine (GlcNAc), galactose (Gal), sialic acid (NeuAc), N-acetylgalactosamine (GalNAc), and fucose (Fuc). Id. at 975-76. These common oligosaccharides are joined to the common core oligosaccharide structure in predictable and well-defined configurations to form mature N-linked oligosaccharides. *See id.*; *see also* Specification at Figure 1 (depicting the typical N-linked oligosaccharide structures, including high mannose, bisected hybrid, bi-antennary complex, bisected bi-antennary complex, tri-antennary complex, tri'-antennary complex, and tetra-antennary complex).

As a further example that the possible glycoforms encompassed by the present invention are finite and not widely variant, Jefferis and Lund show that, for a complex biantennary N-linked oligosaccharide structure in an IgG Fc region, there is only "a total of 36 structurally unique oligosaccharides [that] may be attached at each Asn297

residue." EXHIBIT B at 113. Thus, it is clear from the fact that N-linked oligosaccharides are based on a common core structure and the possible combinations of non-core oligosaccharides are derived from a common pool of sugar residues, the genus of possible N-linked oligosaccharide structures that can be added at the common Asn297 residue in the IgG Fc region is well-defined and finite.

(5) The Genus of Glycosyltransferases is Defined and Finite

The genus of glycoprotein-modifying glycosyltransferases that can be used to glycoengineer the claimed antibodies, likewise, is not infinite or widely variant. For example, as discussed in the priority document (U.S. Provisional Application No. 60/082,581, incorporated by reference in its entirety into the present application), there are only eight Golgi-localized enzymes that are responsible for the distribution of oligosaccharides into the major structural classes of oligosaccharides: ManI, ManII, GalT, GnTI, GnTII, GnTIII, GnTIV, and GnTV. *See, e.g.,* Priority Document at page 14, lines 25-27, page 16, line 4 to page 17, line 8, and at Figure 2 (excerpts attached hereto as EXHIBIT C). In addition, enzymes that catalyze terminal glycosylation reactions, such as fucosyltransferases, galactosyltransferases, and sialytransferases, were known in the art and their mechanisms of action have been characterized. *See, e.g.*, Youakim and Shur, *Annals New York Acad. Sci.* 745: 332-35 (1994) (attached hereto as EXHIBIT D). Furthermore, the reactions catalyzed by known glycosyltransferases (*e.g.*, the oligosaccharide that is added by each glycosyltransferase and the structure to which it is added) have been characterized. *See, e.g.*, Priority Document at page 16, line 4 to page 17, line 8. Thus, the genus of glycosyltransferases that can be used to

glycoengineer the claimed antibodies and their mechanism of action are well-defined and finite.

b) The Claimed Antibodies are More than Adequately Described in the Specification as Filed

Contrary to the assertions set forth in the Office Action, Applicants respectfully submit that the disclosure of the captioned application provides a representative number of cell types and glycosyltransferases such that one of ordinary skill in the art would have understood that the applicants had possession of the claimed invention at the time the application was filed. First, the specification explicitly describes several exemplary mammalian host cell lines. Second, the specification explicitly describes several exemplary glycosyltransferases that can be used to glycoengineer antibodies of the claimed invention to produce the desired increase in ADCC and/or Fc receptor binding. Third, Applicants have shown that expression of various glycosyltransferases will lead to the production of antibodies according to the present claims.

(1) The Specification Describes Several Exemplary Mammalian Host Cell Lines

The specification as filed specifically states that, "[p]referably mammalian cells are used as host cell systems ..." Specification at page 17, lines 29-30. Furthermore, the specification provides that, "[m]sot preferably, CHO cells, BHK cells, NS0 cells, or SP2/0 cells, or alternatively, hybridism cells are used as host cell systems." *Id.* at lines 32-33. Thus, the specification contemplates the use of any type of mammalian cells in accordance with the claimed invention, and expressly provides a representative number of species of mammalian cell types that may be used in accordance with the claimed invention.

A similar situation was addressed by the Federal Circuit in *Amgen*, which held that disclosure of only two species of vertebrate or mammalian cells provided adequate written description support for the entire genus of vertebrate or mammalian cells used to produce glycosylated erythropoietin according to the claimed invention. 314 F.3d at 1398. The court stated that "the words 'vertebrate' and 'mammalian' readily 'convey[] distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of the members of the genus.'" *Id.* (citations omitted). Given that multiple species within the genus of mammalian cell types are explicitly disclosed in the present specification--and certainly more than two as in *Amgen*--and because mammalian cell types share common glycosylation machinery and characteristics that were known in the art, Applicants respectfully submit that a representative number of species was provided such that one of ordinary skill in the art could visualize or recognize the identity of the members of the entire genus.

(2) The Specification Describes Several Exemplary Glycosyltransferases

The specification as filed also specifically discloses how mammalian host cells may be glycoengineered to produce the antibodies of the invention, including providing numerous specific but non-limiting embodiments of the glycoprotein-modifying glycosyltransferases that can be used, as well as combinations of these glycosyltransferases. For example, the specification as filed states that:

> The invention is contemplated to encompass engineered host cells expressing any type of glycoprotein-modifying glycosyl transferase as defined herein. However, in preferred embodiments, at least one glycoprotein-modifying glycosyl transferase expressed by the host cells of the invention is **GnT III, or, alternatively, β(1,4)-N-acetylglucosaminyltransferase V (GnT V).** However, also other types of glycoprotein-modifying glycosyl transferase may be expressed in the host system, typically in addition to **GnT III or GnT V, including β(1,4)-**

> **galactosyl transferase (GalT), and mannosidase II (Man II).** In one embodiment of the invention, **GnT III is coexpressed with GalT.** In another embodiment of the invention, **GnT III is coexpressed with Man II**. In a further embodiment of the invention, **GnT III is coexpressed with GalT and Man II.** However, any other permutation of glycoprotein-modifying glycosyl transferases is within the scope of the invention. Further, expression of a glycosidase in the host cell system may be desired.

Specification at page 13, lines 18-30 (emphasis added). Clearly, the specification as filed contemplates multiple paths to achieve the claimed antibodies. Because the finite and well-defined genus of glycosyltransferases and their mechanisms of action were known in the art, there is no need to describe each one in detail. *See Capon*, 418 F.3d at 1357-58. Thus, Applicants respectfully submit that a representative number of species of glycosyltransferases was described in the specification as filed.

(3) Applicants Have Shown that Expression of Various Glycosyltransferases Will Work

The Office asserts that "[t]here is no evidence provided in the specification that any glycosyltransferases aside from GnTIII, transfected into any cell other than CHO cells would lead to the production of antibodies having the same characteristics as those produced in CHO cells expressing exogenous GnTIII." Office Action at page 4, paragraph 10. Applicants respectfully disagree with this assertion.

First, Applicants respectfully remind the Examiner that an adequate written description does *not* require an applicant to provide examples or actual reduction to practice. *Falkner,* 448 F.3d at 1366. Furthermore, "[d]escription of a representative number of species does <u>not</u> require the description to be of such specificity that it would provide individual support for each species that the genus embraces." MPEP § 2163 at 2100-183. (emphasis added). The specification as filed expressly contemplates the use

of other glycosyltransferases besides GnTIII in other host cells besides CHO cells. Applicants therefore submit that the specification as file provides adequate description of the claimed invention.

Second, Applicants have in fact shown that other embodiments of the invention clearly contemplated by the specification did, in fact, work as described in the specification as filed. *See* Declaration of Pablo Umaña, Ph.D., filed July 18, 2005. Dr. Umaña's Declaration provides evidence, for example, that the co-expression of an antibody with the ManII glycosyltransferase results in antibodies with an increased proportion of non-fucosylated oligosaccharides that show an increase in Fc receptor binding and ADCC activity. *See* Declaration of Dr. Pablo Umaña at pages 2-4 (and references cited therein). Use of the ManII glycosyltransferase was expressly contemplated in the specification as filed: "other types of glycoprotein-modifying glycosyl transferase may be expressed in the host system, typically in addition to GnT III or GnT V, including . . . **mannosidase II (Man II)**." Specification at page 13, lines 23-25 (emphasis added).

Hence, Applicants specifically contemplated in the specification as filed that the invention encompasses a variety of host cells and glycosyltransferases, and have provided evidence that other embodiments of the claimed invention can be achieved as described. Accordingly, Applicants have provided disclosure that is more than sufficient to meet the written description requirement for the claimed invention.

c) The Priority Document is Further Evidence that the Claimed Invention is More than Adequately Described

As further evidence that the claimed invention has sufficient written description support, Applicants point to the priority document, which provides a detailed description

of a physical model for determining heterogeneity of glycoforms that result from processing in the N-linked glycosylation pathway. *See* Priority Document, EXHIBIT C, at Figure 2; at page 3, lines 26-31; at page 16, line 4 to page 18, line 20. In describing the physical model, the priority document explicitly recognizes that widely-used mammalian industrial cell lines such as CHO cells and BHK cells share common features of the central reaction network in the N-linked glycosylation pathway. *Id.* at page 17, lines 9-22. Thus, although the Office contends that "the mention of studies in BHK cells in Example 6 appears to be completely prophetic in nature with evidence that modified BHK cells would produce antibodies that were modified in a similar manner to modified CHO cells," Office Action at page 10, paragraph 4, it is clear that these cells had common features that were known in the art and therefore required no further description. *See Capon*, 418 F.3d at 1357-58.

In describing the physical model of glycosylation, the priority document specifically recognizes that "[t]he addition of fucose to the core of oligosaccharides can take place at any point after reaction 5 of the [central reaction network of the N-linked glycosylation pathway], but it is also blocked by the modifications that *GalT or GnTIII* introduce." Priority Document at page 17, lines 28-30 (emphasis added). Blocking of fucosyltransferase activity would be expected to result in an increase in the proportion of non-fucosylated oligosaccharides in the Fc region. In identifying that this phenomenon can occur with GalT as well as GnTIII, the priority document clearly discloses that there are multiple ways to manipulate glycosyltransferase expression to achieve preferred glycoforms.

The priority document also provides a detailed description of a mathematical model "to calculate the expected qualitative trends in the N-linked oligosaccharide

distribution resulting from changes in the levels of one or more enzymes involved in the network of enzyme-catalyzed reactions which accomplish N-linked oligosaccharide biosynthesis." *Id.* at page 12, lines 9-12. CHO cells were chosen as a specific example for the model "since CHO cells are currently the most common host for the industrial production of therapeutic glycoproteins." *Id.* at page 13, lines 6-7. However, as specifically recognized in the priority document, the "[v]alues for the parameters in the model and their normal ranges can either be found in the literature or estimated from literature information." *See id.* at page 12, line 14 to page 13, line 9.

These physical and mathematical models further support what is disclosed in the specification as filed; namely, that recombinant, glycoengineered antibodies with desired properties (*e.g.*, increased ADCC and/or increased Fc receptor binding) can be achieved by manipulating the expression of various enzymes in the N-linked glyocosylation pathway in mammalian host cells. The choice of the enzymes to be manipulated for production of a preferred glycoform can be made based on the known activity of the enzymes (*e.g.* the oligosaccharide they will attach to a given residue on the core oligosaccharide structure) and the machinery that exists in the chosen mammalian host cell such that a desired glyocsylation profile is achieved. These parameters are either known, or can be determined readily from the knowledge in the art. As such, the disclosure of the present application provides more than ample written description support.

d) The Level of Knowledge in the Art was High

The Office contends that "glycosylation patterns due to unmodified cells and indeed the differences that could be expected with modification by different glycosyltransferases remains unclear and complex at the time the invention was made,

and that further studies with evidence are necessary to investigate the functional roles of different glycosyltransferases in different cell types." Office Action at page 5, paragraph 11. Applicants respectfully disagree with this contention. Applicants respectfully submit that the Office has not properly considered the knowledge in the art regarding glycosylation in mammalian cells.

(1) Lifely* et al., *Does Not Represent Lack of Knowledge in the Art

The Office points to Lifely *et al.*, *Glycobiology* 5: 813-822 (1995), in particular, as representative of the state of the art, and contends that "Lifely [] teaches that recombinant antibodies produced in different cell types result in antibodies having distinct glycosylation patterns and distinct levels of ADCC-induction []. Thus Lifely clearly teaches that different cells produce differentially glycosylated recombinant antibodies." Office Action at page 4, paragraph 10.

While Applicants do not disagree that Lifely *et al.* disclose that differentially glycosylated antibodies can be produced in different unmodified cell types, Applicants respectfully disagree with the conclusion drawn by the Office that Lifely *et al.* represents evidence of the lack of written description for the presently claimed invention: quite to the contrary, if anything, Lifely *et al.* provide evidence that there existed at the time of filing of the captioned application knowledge in the art that the glycosylation profiles generated by the endogenous glycosylation machinery of various unmodified mammalian host cells was either known (e.g., CHO, Y0, and NS0 cells), or readily capable of being characterized by methods known in the art, and as such, do not require re-description in the captioned application. Applicants' invention shows how to

manipulate that machinery through glycoengineering to achieve antibodies with desired glycosylation profiles and resultant desired properties (*e.g.*, increased ADCC).

(2) The Ability to Manipulate Glycosylation Machinery was Known

Applicants have already shown, *supra*, that the knowledge in the art was of a level such that Applicants are not required to describe everything that was already known about glycosylation in mammalian cells. Furthermore, there was knowledge in the art to indicate that manipulation of the glycosylation machinery in cells of various types to achieve a preferred glycosylation profile was possible. For example, Grabenhorst *et al.*, *Glycoconjugate J.* 16: 81-97 (1999) (attached hereto as EXHIBIT E), which published shortly after the filing date of the present application, comments on studies in glycosylation for the preceding decade, and describes the advances in the art to that point. *See id.* at page 82, column 1.

Grabenhorst *et al.* recognized that, "...during the past 12 years much work has been published on the *structural characterization* of recombinant glycoproteins expressed from various *mammalian and nonmammalian expression systems*." *Id.* (emphasis added). They further stated that "a great deal of efforts is presently going into attempts to improve recombinant host cell lines, and here especially, mammalian cells, for the manufacturing of glycoprotein pharmaceuticals ... with novel *in vivo* properties." *Id.* Based on their observations, they provide a model for

> the recombinant expression of the full length form of human glycosyltransferases along with a suitable reporter glycoprotein (here human β-TP) at a constant epxpression level in a heterologous mammalian host cell line that is devoid of the pertinent enzyme activity. **This is considered to represent a valuable model and should enable the comparison of the *in vivo* specificities of different members of a glycosyltransferase family [citations omitted] and allow the selection of the optimal enzyme suitable for the glycosylation engineering of**

> **host cell lines** for the production of a new generation of glycotherapeutics with defined altered glycosylation characteristics.

Id. at 87 (emphasis added).

With respect to knowledge of mammalian host cells used for recombinant expression of human therapeutic glycoproteins, Grabenhorst *et al.* state that "over the past 12 years the literature reporting on the glycosylation analysis of recombinant glycoproteins from different hosts has accumulated tremendously." *Id.* at page 82, column 1. They further state that, "[a]s has become clear from the work of others and our own investigations, CHO and BHK-21 cells show basically the same characteristics for the glycosylation of recombinant N- or O-glycoproteins." *Id.* at column 2. Grabenhorst *et al.* also provide a table (Table 1) summarizing the structural features of N-linked oligosaccharides from recombinant glycoproteins expressed in different types of mammalian host cells (*i.e.*, hamster cell lines CHO and BHK-21, and murine cell lines C127 and Ltk-). *Id.*

Grabenhorst *et al.* also recognized that advances in methods used to study glycosylation were known in the art:

> [s]ignificant advances in the sensitivity of carbohydrate structural analysis has [sic] been achieved during the past three years. Especially in mass spectrometry (on-line ESI-MS, nanospray tandem mass spectrometry (ESI-MS/MS) and improved MALDI/TOF techniques), very sensitive instrumentation for glycosylation analysis has been made available to a broader group of research units, and thus has led to a broader use of complementary tools by academic researchers and in industrial laboratories.

Id. at page 83, col. 1.

Thus, Grabenhorst *et al.* emphasize the fact that there was knowledge in the art regarding the manipulation of glycosylation machinery to achieve preferred glycoprotein glycoforms from which models could be developed, and that the tools for such manipulation (cell types, glycosylation structures, detection methods, etc.) were also known in the art.

e) Summary

Given the knowledge in the art as discussed above, Applicants are not required to include in the specification all that was known in the art with respect to glycosylation in mammalian cells in order to provide sufficient written description. Rather, the specification as filed describes a representative number of species sufficient to indicate that the Applicants had possession of the claimed invention.

To the extent that the Office suggests that Applicants are required to provide a common structure and/or some functional relationship to a structure in order to provide adequate written description, *see* Office Action at pages 5-6, paragraphs 11-12, Applicants respectfully reiterate that "there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner,* 448 F.3d at 1366 (Fed. Cir. 2006). In the present case, Applicants respectfully submit that, as shown in detail by the foregoing discussion, since the structures related to the claimed invention (*e.g.*, of the mammalian cells, the IgG Fc regions, the oligosaccharides, and the glycosyltransferases) were known in the art, it is not necessary to explicitly recite each one in detail in the specification. *Id.*

For the above reasons, Applicants respectfully submit that, in the present case, the written description requirement of 35 U.S.C. § 112, first paragraph is met.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Withdrawal of Previous Rejections

1. The Rejections Under 35 U.S.C. §§ 102 and 103

Applicants thank the Examiner for withdrawing the rejections under 35 U.S.C. §§ 102 and 103. *See* Office Action at 2.

2. Previous Rejection under 35 U.S.C. § 112, First Paragraph Withdrawn

Applicants would like to thank the Examiner for withdrawing the rejection of the claims under 35 U.S.C. § 112, first paragraph, for an alleged lack of enablement. However, for the sake of completeness, Applicants would like to address the comments made regarding the Declaration filed with Applicants' Reply on July 18, 2005. Specifically, the Office Action stated that the Declaration was insufficient to overcome the rejection of the claims under 35 U.S.C. § 112, first paragraph, set forth in the last Office Action because the references cited therein were not available until after the effective filing date of the captioned application. *See* Office Action at page 2, paragraph 2.

Applicants respectfully submit that the dismissal of the evidence provided in the Declaration on these grounds is incorrect. While Applicants agree that a specification must be enabling as of the filing date (which the present specification was), post-filing publications can be used to demonstrate that the disclosure was enabling. *See Amgen* 314 F.3d at 1336 (holding that district court did not error in finding "that a skilled artisan could readily have used various cultured vertebrate and animal cells to produce human EPO, [when] this fact was buttressed by numerous post-filing publications that demonstrated the extent of the enabling disclosure"). Furthermore, the MPEP

specifically provides that an applicant is not precluded "from providing a declaration *after the filing date* which demonstrates that the claimed invention works." MPEP § 2164.05 (Rev. 3, Aug. 2005) at 2100-198 (emphasis added). Applicants respectfully point out that the references provided with the Declaration of Dr. Pablo Umaña were provided for this very reason: *i.e.*, as post-filing evidence to demonstrate that the techniques taught in the captioned application can be used to produce glycoengineered antibodies having increased binding affinity for Fc receptors. As such, the Declaration of Dr. Umaña provides probative evidence of enablement, even though the exhibits provided therewith were published after the filing date of the captioned application.

C. Rejections for Double-Patenting

At pages 6-10 of the Office Action, the Office has provisionally rejected various claims for double patenting over claims of Applicants' copending applications. Applicants respectfully request that this rejection be held in abeyance until otherwise allowable claims are identified, at which time Applicants will consider filing a Terminal Disclaimer.

Conclusion

Prompt and favorable consideration of this Reply is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Timothy J. Shea, Jr.
Attorney for Applicants
Registration No. 41,306

Date: July 24, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600